Longitudinal Arrhythmic Risk Assessment Based on Ejection Fraction in Patients with Recent-Onset Nonischemic Dilated Cardiomyopathy

Giulia De Angelis, MD, Marco Merlo, MD, Giulia Barbati, PhD, Silvia Bertolo, MD, Antonio De Luca, MD, Federica Ramani, MSc, Luigi Adamo, MD, PhD, and Gianfranco Sinagra, MD, FESC, *Trieste, Italy; Baltimore, Maryland*

Background: Practice guidelines suggest the use of implantable cardioverter-defibrillators in patients with left ventricular ejection fractions (LVEF) ≤ 35% despite 3 to 6 months of guideline-directed medical therapy (GDMT). It remains unclear whether this strategy is appropriate for patients with dilated cardiomyopathy (DCM), who can experience reverse ventricular remodeling for up to 24 months after the initiation of GDMT. The aim of this study was to assess the longitudinal dynamic relationship between LVEF ≤ 35% and arrhythmic risk in patients with recent-onset nonischemic DCM on GDMT.

Methods: A retrospective analysis was conducted among patients with recent-onset DCM (≤6 months) and recent initiation of GDMT (≤3 months) consecutively enrolled in a longitudinal registry. Risk for major ventricular arrhythmic events or sudden cardiac death was assessed in relationship to LVEF ≤ 35% at enrollment and 6 and 24 months after initiation of GDMT.

Results: Five hundred forty-four patients met the inclusion criteria. LVEF ≤ 35% identified patients with increased risk for major ventricular arrhythmic events or sudden cardiac death starting from 24 months after initiation of GDMT (hazard ratio, 2.126; 95% CI, 1.065-4.245; *P* = .03). However, LVEF ≤ 35% at presentation or 6 months after enrollment did not have prognostic significance. Sixty-seven percent of 131 patients with LVEF ≤ 35% at 6 months after initiation of GDMT had improved LVEFs (to >35%) by 24 months. This late LVEF improvement correlated with lower arrhythmic risk (*P* = .012) and was preceded by a reduction of LV dimensions in the first 6 months of GDMT.

Conclusions: In patients with DCM, the present findings suggest that risk stratification for major ventricular arrhythmic events or sudden cardiac death on the basis of LVEF ≤ 35% is effective after 2 years of GDMT, but not after 6 months. In selected patients with DCM, it would be appropriate to wait 24 months before primary prevention ICD implantation. (J Am Soc Echocardiogr 2022;35:801-9.)

Keywords: Dilated cardiomyopathy, Sudden cardiac death, Arrhythmic stratification, Implantable cardioverter-defibrillator, Prognosis

Abbreviations

DCM = Dilated cardiomyopathy

GDMT = Guideline-directed medical therapy

HMDR = Heart Muscle Disease Registry

HR = Hazard ratio

ICD = Implantable cardioverter-defibrillator

LV = Left ventricular

LVEDDi = Indexed left ventricular end-diastolic diameter

LVEF = Left ventricular ejection fraction

LVRR = Left ventricular reverse remodeling

MR = Mitral regurgitation

MVA = Major ventricular arrhythmia

RV = Right ventricular

SCD = Sudden cardiac death

VT = Ventricular tachycardia

Patients with left ventricular ejection fractions (LVEF) ≤ 35% have been shown to benefit from implantable cardioverter-defibrillators (ICDs).[1] Therefore, practice guidelines suggest the placement of ICDs for primary prevention in patients in New York Heart Association functional class < IV with LVEFs ≤ 35% after ≥3 months of guideline-directed medical therapy (GDMT).[2] However, recent evidence has called into question the efficacy of primary prevention ICDs on the basis of these cutoffs in patients with nonischemic cardiomyopathy.[3] This led to the downgrading of class of recommendation for ICD placement in this patient category in the very recent European guidelines on the management of heart failure.[2] In fact, 40% to 50% of patients with nonischemic dilated cardiomyopathy (DCM) experience significant left ventricular reverse remodeling (LVRR) and marked improvement of LVEF during the first 12 to 24 months of GDMT.[4] This raises the concern that a significant proportion of ICDs in patients with DCM might be unwarranted or even harmful.[5]

To address this area of uncertainty, we designed a retrospective cross-sectional analysis of a well-characterized registry of consecutive patients with recent-onset DCM, with the goal of investigating the risk for major arrhythmic events during the first 2 years of GDMT and its relationship to LVEF higher or lower than 35%.

METHODS

Study Population and Design

All patients with DCM consecutively enrolled in the Heart Muscle Disease Registry (HMDR) of Trieste between January 1, 1993, and December 31, 2017, were retrospectively reviewed. The HMDR has been previously described.[6] The registry defines DCM as the presence of left ventricular (LV) systolic dysfunction (LVEF ≤ 50%) in the absence of either pressure or volume overload or significant coronary artery disease.[7] Coronary angiography or coronary computed tomography is performed in patients >35 years old and in those with cardiovascular risk factors to exclude significant coronary artery disease. Patients with active myocarditis were excluded from this analysis. Patients with DCM enrolled in the registry received GDMT.[6] When clinically indicated, an ICD or a cardiac resynchronization therapy device and defibrillator was implanted during follow-up.

For the present analysis we identified within the HMDR all patients with DCM meeting both of the following criteria: (1) recent-onset DCM, defined as symptoms with duration ≤6 months before enrollment, and (2) initiation of GDMT ≤3 months before enrollment.

Data recorded at the time of enrollment (i.e., the first evaluation in the University of Trieste Heart Failure Clinic) and data available at the scheduled 6- and 24-month follow-up evaluations were analyzed as key time points. The first temporal cut point (6 months, ranging from 3 to 9 months) was based on the actual indication of a waiting period of ≥3 months in GDMT for primary prevention ICD placement[2] and has already been proposed as an ideal timing for follow-up of patients with DCM.[8] The second temporal cut point (24 months, ranging from 12 to 36 months) was based on the evidence that LVRR takes on average ≥ 12 to 24 months to complete.[8]

The study was reviewed and approved by the institutional review board of the University of Trieste. All patients provided informed consent for the enrollment in the registry.

Echocardiographic Evaluation

Echocardiographic analysis was performed according to international guidelines[9] and in line with the following standardized protocol. In brief, LV diameters were measured in the parasternal long-axis view, perpendicular to the LV long axis at the level of the mitral valve leaflet tips. LV volumes and LVEF were calculated using the biplane method of Simpson. Measurements were normalized to body surface area. Transmitral E- and A-wave velocities were measured using pulsed-wave Doppler at the level of the mitral valve leaflet tips. The LV filling pattern was classified as restrictive in the presence of an E-wave deceleration time < 150 msec and an E/A ratio ≥ 2.[10] Right ventricular (RV) dysfunction was defined by RV fractional area change < 35% or tricuspid annular plane systolic excursion < 18 mm. Mitral regurgitation (MR) was assessed using a multiparametric approach.[11] The interoperator variability of our laboratory for DCM echocardiograms has been previously reported.[12]

A set of "dynamic parameters" was defined by analyzing changes between images collected at the time of enrollment and at 6-month follow-up and included (1) MR reduction or persistence of mild or absent MR, defined as reduction of MR grade from moderate or severe to mild or absent, or the persistence of mild or absent MR; (2) indexed LV end-diastolic diameter (LVEDDi) reduction, defined[4] as a decrease in LVEDDi of ≥10% or to an LVEDDi ≤ 33 mm/m^2; (3) LVEF improvement, defined as an increase in LVEF of ≥10 points[4]; (4) restrictive filling pattern disappearance; and (5) RV function normalization or persistence of normal RV function.

Study Design and Outcomes

The study was divided into two phases as outlined in Figure 1.

Phase 1 included all patients meeting the inclusion criteria and was focused on defining the longitudinal arrhythmic risk of patients with DCM during the first 2 years of GDMT and its relationship to LVEF ≤ 35% or >35%. For the purposes of this analysis, the composite of major ventricular arrhythmias (MVAs) and sudden cardiac death (SCD) during follow-up was considered the outcome of interest. SCD was defined as unexpected death occurring ≤1 hour after symptom onset in the absence of cardiac deterioration, during sleep, or ≤24 hours after last being seen alive.[13] MVAs included successfully resuscitated ventricular fibrillation or ventricular tachycardia (VT), sustained (>30 s) VT causing hemodynamic instability or appropriate ICD interventions, defined as shock or antitachycardia pacing for termination of rapid (>185 beats/min) sustained VT or ventricular fibrillation.[14]

HIGHLIGHTS

- Primary prevention ICD indications in nonischemic DCM are still a matter of debate.
- Strategies based on LVEF after 3 months of therapy failed to demonstrate efficacy.
- Twenty-four months may be better for evaluation of DCM patients for ICD implantation.
- Early reduction of LV diameter on therapy identifies patients improving LVEF to >35%.
- Such late improvement is associated with lower long-term arrhythmic risk.

Phase 2 was prompted by the findings from phase 1 and included the subgroup of patients with persistent LVEF ≤ 35% at 6 months and available echocardiographic data at 24 months. Phase 2 was focused on (1) confirming the accuracy of risk stratification for MVAs or SCD on the basis of LVEF at 24 months in patients with persistent LVEF ≤ 35% at 6-month follow-up and (2) identifying early predictors of "late" improvement of LVEF to >35% (i.e., LVEF ≤ 35% at 6 months and >35% at 24 months).

The end of follow-up was defined as the date of event adjudication or December 31, 2020. When multiple events occurred, patients were censored at the time of the first event.

Statistical Analysis

Summary statistics of clinical and instrumental continuous variables are expressed as mean ± SD. Comparisons between groups were made using two-tailed t tests for continuous variables and χ^2 exact tests for categorical variables.

For phase 1 of the study, cumulative incidence curves for the composite end point of MVAs or SCD were estimated and compared between groups, using a competing-risks analysis,[15] taking into account competing risks for non-SCD plus heart transplantation plus durable LV assist device implantation. A landmark analysis was also performed. Curves were computed starting from enrollment in the registry and then in a landmark approach restarting from the subsequent key time points (i.e., from the 6- and 24-month evaluations), conditionally to having survived until the landmark and having LVEF evaluation available at the landmark.

For phase 2 of the study, univariable and multivariable logistic regression models were built to explore the association of the variables of interest with "late" improvement of LVEF. Parameters with *P* values ≤ .10 in the univariable analyses were inserted as candidate predictors in a multivariable model. Analyses were conducted using SPSS version 24 (IBM, Armonk, NY) and R (R Foundation for Statistical Computing, Vienna, Austria) using the package cmprisk.

RESULTS

Phase 1: Risk for Major Arrhythmic Events during the First 2 Years of GDMT

Among 1,207 patients with DCM consecutively enrolled in the HMDR of Trieste during the study period, 544 met the inclusion criteria and had echocardiographic data available at enrollment, 355 (65%) had echocardiographic data collected at the 6-month evaluation (median, 5 months; interquartile range, 3-6 months), and 403 (73%) had echocardiographic data collected at the 24-month evaluation (median, 24 months; interquartile range, 19-28 months). Data from all these patients were included in the competing-risk landmark analysis (phase 1, Figure 1). The main characteristics of these patients at the three time points are reported in Table 1. During follow-up, 82 patients (15%) underwent ICD implantation and 51 (9%) underwent cardiac resynchronization therapy device and defibrillator implantation. Among 544 patients enrolled, 57 (11%) experienced major arrhythmic events: 14 (3%) experienced SCD, 38 (7%) experienced appropriate ICD interventions, and five (1%) had ventricular fibrillation or hemodynamically unstable VT. Among patients with appropriate ICD interventions, 20 (4%) were antitachycardia pacing and 18 (3%) were shocks. Median time to ICD intervention was 50 months (interquartile range, 25-75 months). Starting from enrollment, the cumulative incidence of MVAs or SCD during the first 6 months was 0.2% for patients with LVEFs ≤ 35% and 0.7% for those with LVEFs > 35% (unadjusted hazard ratio [HR], 0.342; 95% CI, 0.047-2.473; *P* = .288). Starting from the 6-month time point, the cumulative incidence of MVAs or SCD up to the 24-month time point was 3.2% for those with LVEFs ≤ 35% and 2.1% for those with LVEFs > 35% (unadjusted HR, 1.875; 95% CI, 0.313-11.227; *P* = .491). Finally, starting from the 24-month time point, the cumulative incidence of MVAs or SCD up to 60 months since enrollment was 12.4% for those with LVEFs ≤ 35% and 4.1% for those with LVEFs > 35% (unadjusted HR, 2.126; 95% CI, 1.065-4.245; *P* = .032). The 24-month time point was the first time point during follow-up at which LVEF ≤ 35% was able to identify patients with DCM with higher arrhythmic risk during the subsequent follow-up, with a prompt separation of the cumulative, competing risk–adjusted incidence curves (Figure 2).

Phase 2: Late LVEF Improvement after Initiation of GDMT and Risk for MVAs or SCD

As stated above, LVEF ≤ 35% was associated with MVAs or SCD starting from the 24-month evaluation. However, current guidelines recommend ICD in patients with DCM with LVEFs ≤ 35% and New York Heart Association functional class < IV after 3 to 6 months of GDMT. We therefore decided to focus on the subgroup of 136 patients with LVEFs ≤ 35% and New York Heart Association class < IV at the 6-month evaluation and available data at the 24-month evaluation in order to understand how many patients identified as "high risk" (on the basis of LVEF ≤ 35% at 6 months) would move to a "low risk" group (on the basis of LVEF > 35% at 2 years; phase 2, Figure 1). Five patients who underwent cardiac resynchronization therapy device and defibrillator implantation between the 6- and 24-month evaluations were excluded from this analysis to avoid possible bias introduced by the effect of cardiac resynchronization therapy on reverse cardiac remodeling. Among 131 patients, 88 (67%) had improved LVEFs (to >35%) between the 6- and 24-month evaluations (i.e., experienced "late" LVEF improvement), reaching a mean LVEF of 44% (Supplemental Figure 1).

The main characteristics of those 131 patients at the time of enrollment and at the 6-month evaluation are presented in Supplemental Table 1 and Table 2, respectively. Patients with "late" LVEF improvement were confirmed to have a lower rate of MVAs or SCD during follow-up compared with those with persistent LVEF ≤ 35% (0% vs 7.7% at 1 year and 4.4% vs 18.5% at 4 years in patients with "late" LVEF improvement vs patients with persistent severe LV dysfunction, respectively; unadjusted HR, 3.750; 95% CI, 1.340-10.496; *P* = .012). Notably, the risk for adverse events in the two groups diverged soon after the 24-

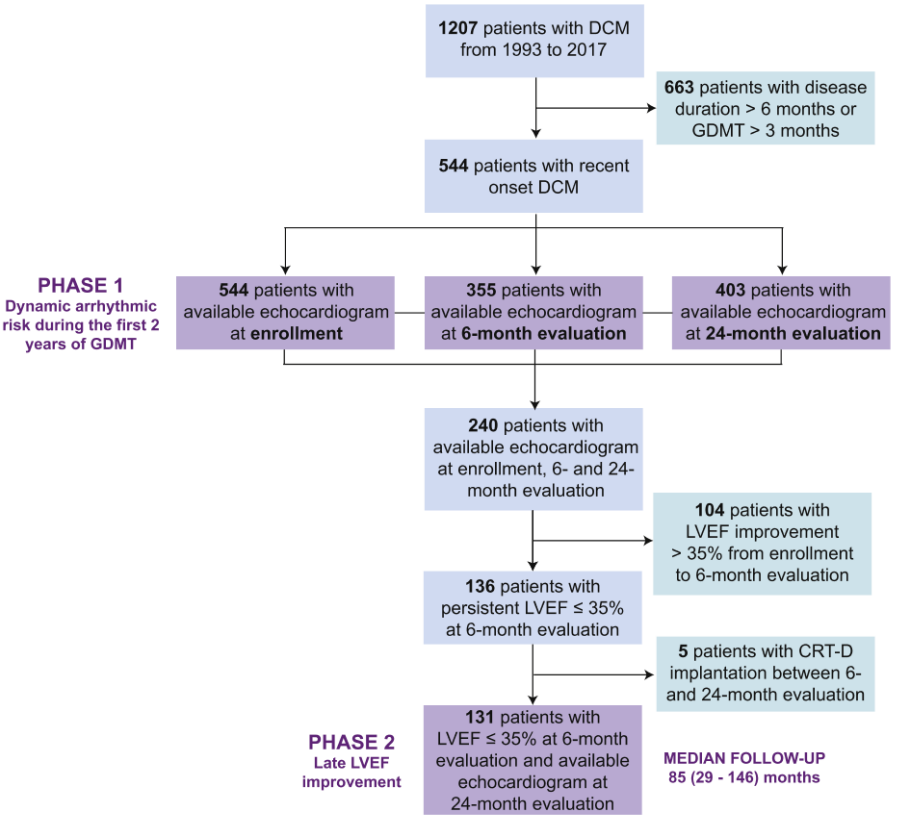


Figure 1 Study design and study population. Patients with recent-onset DCM were selected from the HMDR and enrolled in phase 1 of the study. A selected subpopulation with available data at all three key time points and LVEF ≤ 35% at 6 months was enrolled in phase 2. *CRT-D*, Cardiac resynchronization therapy and defibrillator.

month evaluation, further confirming the value of LVEF-based arrhythmic risk stratification after 24 months of GDMT (Figure 3).

Predictors of Late LVEF Improvement in Recent-Onset DCM

We hypothesized that the presence or absence of "late" LVEF improvement was the result of a difference in response to GDMT that could be identified early through echocardiographic assessments. At the 6-month evaluation, patients who ended up experiencing "late" LVEF improvement had slightly higher LVEFs than patients who did not (29 ± 5% vs 26 ± 6%, respectively, $P = .02$), smaller LV dimensions (LVEDDi 34 ± 5 vs 37 ± 4 mm/m^2, $P = .01$), and a lower prevalence of moderate or severe MR (18 [21.2%] vs 17 [39.5%], $P = .03$; Table 2). We further investigated the dynamic

Table 1 Characterization of the overall populations selected for the landmark analysis of arrhythmic risk at enrollment, 6 months, and 24 months (phase 1 of the study)

	Patients with available echocardiograms at enrollment (n = 544)	Patients with available echocardiograms at 6 mo (n = 355)	Patients with available echocardiograms at 24 mo (n = 403)
Sex, male	385 (70.8)	248 (69.9)	288 (71.5)
NYHA functional class III or IV	144 (26.5)	21 (5.9)	19 (4.7)
LVEF, %	30 ± 10	38 ± 11	44 ± 11
LVEF ≤ 35%	400 (73.5)	160 (45.1)	91 (22.6)
LVEDDi, mm/m^2	35 ± 5	33 ± 5	31 ± 5
RFP	134 (24.6)	16 (4.5)	12 (3)
Moderate to severe MR	198 (36.4)	71 (20)	52 (12.9)
β-blockers	494 (90.8)	336 (94.6)	368 (91.3)
ACE inhibitors/ARBs/ARNIs	527 (96.9)	349 (98.3)	395 (98.0)

Data are expressed as number (percentage) or as mean ± SD.
ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor/neprilysin inhibitor; *NYHA*, New York Heart Association; *RFP*, restrictive filling pattern.

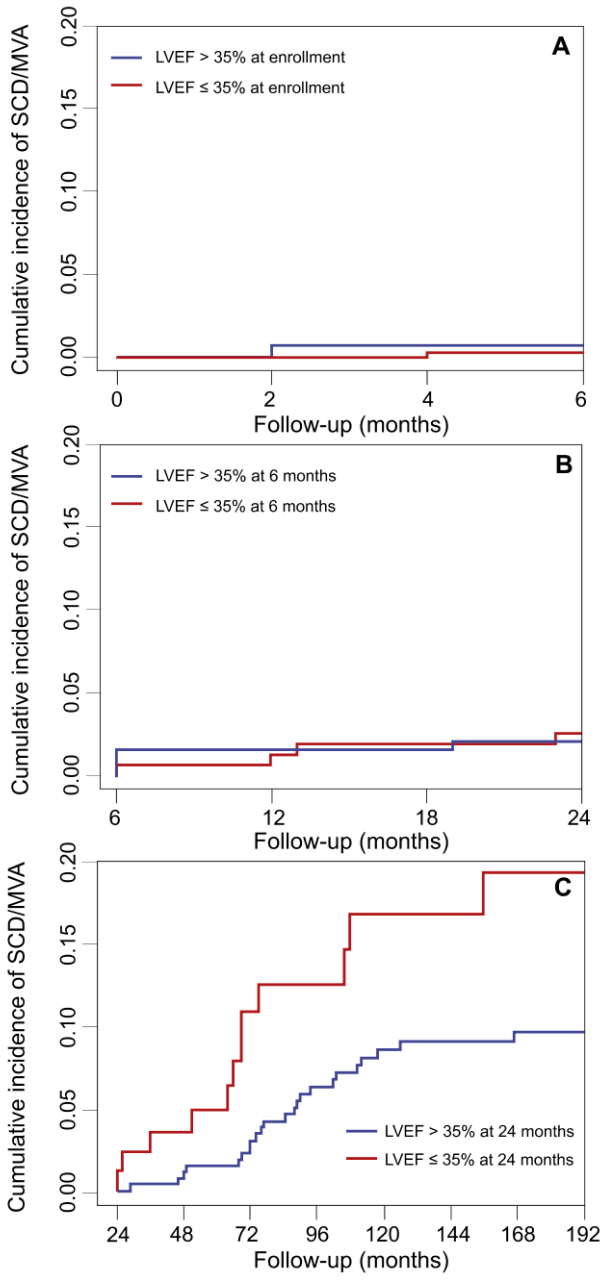


Figure 2 Landmark analysis: cumulative incidence curves for the occurrence of the composite of MVAs or SCD according to LVEF ≤ 35% or >35% at different time points, taking into account competing risk for events (phase 1 of the study). **(A-C)** Cumulative incidence of MVAs or SCD in patients with LVEFs ≤ 35% versus patients with LVEFs > 35% in study phase 1: **(A)** 0.2% versus 0.7% from enrollment to 6 months (HR, 0.342; 95% CI, 0.047-2.473; $P < .05$), **(B)** 3.2% versus 2.1% from 6 to 24 months (HR, 1.875; 95% CI, 0.313-11.227; $P < .05$), and **(C)** 12.4% versus 4.1% from 24 to 60 months (HR, 2.126; 95% CI, 1.065-4.245; $P = .032$).

changes in echocardiographic parameters between baseline and the 6-month evaluation. Patients with "late" LVEF improvement were more likely to have experienced signs of reverse remodeling in the first 6 months of GDMT. In particular, "late" LVEF improvement was associated with MR improvement or persistence of mild or absent MR between enrollment and the 6-month time point (66 [78.6%] vs 25 [59.5%], $P = .02$) and significant reduction in LVEDDi in the same time frame (25 [32.1%] vs 3 [7.5%], $P = .003$; Table 2, Supplemental Figure 2). In a multivariable analysis, including echocardiographic parameters at the 6-month evaluation and dynamic echocardiographic parameters (i.e., changes in echocardiographic parameters between baseline and 6 months after initiation of GDMT), the reduction of the LVEDDi between enrollment and the 6-month evaluation was the only feature independently associated with "late" LVEF improvement (adjusted odds ratio, 4.92; 95% CI, 1.35-17.84; $P = .015$; Table 3). Among the 28 patients with LVEDDi reduction, 25 (89%) had subsequent late LVEF improvement. Among the 91 patients with no LVEDDi reduction, only 53 (58%) experienced late LVEF improvement (Supplemental Table 2). When comparing the occurrence of arrhythmic events after 24 months between patients with and without LVEDDi reduction, a trend toward lower risk in those with LVEDDi reduction was detected (1 [4%] vs 13 [14%], $P = .183$; Table 4).

DISCUSSION

We provide for the first time a longitudinal assessment of arrhythmic risk in a large and well-characterized cohort of patients with recent-onset nonischemic DCM treated with GDMT. We found that (1) before 24 months, the occurrence of MVAs or SCD in patients with DCM is rare and is not associated with LVEF ≤ 35%, but conversely, after 2 years of GDMT, LVEF ≤ 35% portends a higher arrhythmic risk during follow-up (Figures 2 and 3); (2) a high proportion of patients (>60%) have improved LVEFs (to >35%) between 6 and 24 months of GDMT (i.e., "late" LVEF improvement); and (3) a reduction of LV dimensions in the first 6 months of GDMT is strongly associated with subsequent "late" LVEF improvement (Table 3).

These findings suggest that the timing for ICD placement proposed by current guidelines for the treatment of patients with heart failure with reduced ejection fraction might be inappropriate for patients with DCM and that serial analysis of LV dimensions in the first 6 months of GDMT might be a useful tool for the identification of patients with late improvement of LVEF and consequent lower arrhythmic risk. In these patients, ICD placement might be deferred. Given the retrospective nature of the analysis and the highly selective nature of the study, our observations should be seen as hypothesis generating. Future studies with larger populations and prospective design will be needed to confirm our findings.

Long-Term Arrhythmic Risk According to the Time Point of LVEF Evaluation

Several authors have suggested that arrhythmic risk stratification in nonischemic DCM cannot rely only on early assessment of LVEF ≤ 35%, especially after the publication of the DANISH trial.[3,16] Very recently, European guidelines proposed a change in class of recommendation for primary prevention ICDs from I (Level of Evidence: B) to IIa (Level of Evidence: A) in patients with LVEFs ≤ 35% of nonischemic etiology.[2] This area of uncertainty underscores the need to generate additional data to improve risk stratification for MVAs or SCD in patients with DCM.

We found that the risk for MVAs or SCD in patients with DCM is very low in the first 24 months after initiation of GDMT. This finding corroborates the results of the DANISH trial, which reported a low prevalence of SCD in the first 2 years.[3] Furthermore, in our DCM population, LVEF-based arrhythmic risk stratification after 6 months

Table 2 Six-month characterization of patients with LVEFs ≤ 35% at 6-month evaluation and available 24-month evaluation, according to late LVEF improvement (phase 2 of the study)

	Available data	Total (*N* = 131)	LVEF > 35% at 24 mo (*n* = 88)	LVEF ≤ 35% at 24 mo (*n* = 43)	*P*
Age, y	131	53 ± 14	52 ± 14	54 ± 14	.52
Sex, male	131	97 (74.0)	65 (73.9)	32 (74.4)	.95
Familial DCM*	131	20 (15.3)	13 (14.8)	7 (16.3)	.82
SBP, mm Hg	125	122 ± 16	123 ± 15	121 ± 18	.57
DBP, mm Hg	125	75 ± 10	75 ± 9	74 ± 11	.74
HR, beats/min	131	67 ± 11	68 ± 11	65 ± 13	.31
NYHA functional class III or IV	107	7 (6.5)	5 (6.9)	2 (5.7)	.81
Serum hemoglobin, g/dL	109	14.0 ± 3.6	13.6 ± 1.4	15.2 ± 6.2	.12
Serum creatinine, mg/dL	109	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	.6
LBBB	102	27 (26.5)	16 (23.5)	11 (32.4)	.34
LVEF, %	131	**28 ± 6**	**29 ± 5**	**27 ± 6**	**.02**
LVEDDi, mm/m^2	123	**35 ± 5**	**34 ± 5**	**37 ± 4**	**.01**
LVEDVi, mL/m^2	131	**89 ± 34**	**84 ± 29**	**101 ± 42**	**.01**
RFP	125	8 (6.4)	4 (4.7)	4 (10.0)	.26
Moderate to severe MR	128	**35 (27.3)**	**18 (21.2)**	**17 (39.5)**	**.03**
Time from GDMT initiation, mo	131	5.0 ± 2.1	4.8 ± 2.1	5.4 ± 2.1	.16
Therapy					
β-blockers	119	110 (92.4)	76 (95.0)	34 (87.2)	.13
ACE inhibitors/ARBs/ ARNIs	119	113 (95.0)	78 (97.5)	35 (89.7)	.07
Dynamic parameters*					
RV systolic function normalization or persistence of normal RV function*	109	92 (84.4)	59 (84.3)	33 (84.6)	.96
RFP disappearance*	123	115 (93.5)	80 (95.2)	35 (89.7)	.25
MR improvement or persistence of mild/absent MR*	126	**91 (72.2)**	**66 (78.6)**	**25 (59.5)**	**.02**
LVEF improvement*	131	30 (22.9)	21 (23.9)	9 (20.9)	.7
LVEDDi reduction*	119	**28 (23.7)**	**25 (32.1)**	**3 (7.5)**	**.003**

Bold indicates statistically significant parameters.
Data are expressed as mean ± SD or as number (percentage).
ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor/neprilysin inhibitor; *DBP*, diastolic blood pressure; *HR*, heart rate; *LBBB*, left bundle branch block; *LVEDVi*, indexed LV end-diastolic volume; *NYHA*, New York Heart Association; *RFP*, restrictive filling pattern; *SBP*, systolic blood pressure.
*At least one first-degree relative affected or SCD in a first-degree relative ≤35 years old. All dynamic parameters were evaluated as change from enrollment to the 6-month evaluation. MR improvement refers to a reduction of MR grade from moderate or severe to mild or absent.

of GDMT misclassified about two thirds of patients. In fact, 67% of patients with LVEFs ≤ 35% at the 6-month evaluation had improved LVEFs (to >35%) by the 24-month time point, transitioning to a "low-risk" category. This suggests that current guidelines overestimate arrhythmic risk in patients with DCM and likely result in the inappropriate, potentially harmful, placement of a large number of ICDs in this patient population.[5]

In our cohort, the traditional LVEF cutoff of >35% versus ≤35% became an effective tool for arrhythmic risk stratification of patients with DCM when assessed after 24 months of GDMT. This finding likely reflects the fact that patients with DCM on GDMT undergo LVRR for up to 24 months[4,8] and that the biological significance of LVEF ≤ 35% might be reduced until the process of LVRR is completed.

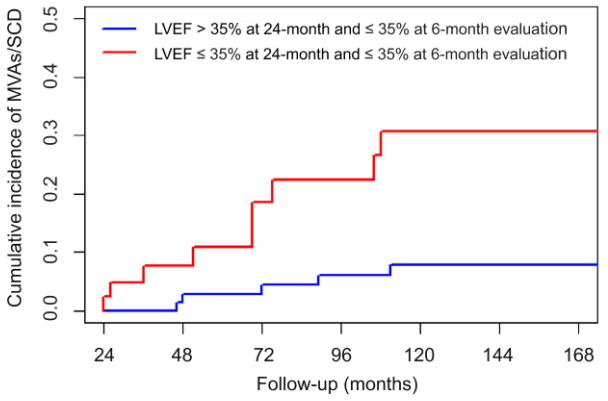


Figure 3 Patients with LVEFs ≤ 35% at 6-month evaluation and available 24-month evaluation (phase 2 of the study): cumulative incidence curves, starting from the 24-month evaluation, for the composite end point of MVAs or SCD according to late LVEF improvement. Cumulative incidence of MVAs or SCD in patients with late LVEF improvement versus patients without: 0.0% versus 7.7% at 12 months and 4.4% versus 18.5% at 4 years, respectively (HR, 3.750; 95% CI, 1.340-10.496; *P* = .012).

Improving Arrhythmic Stratification through Dynamic Evaluation

As we found that the risk for MVAs or SCD is low in patients with DCM in the first 2 years of GDMT, it might be conceivable to wait for 24 months of GDMT before stratifying patients with DCM on the basis of LVEF. However, 2% to 3% of patients in our study cohort experienced adverse arrhythmic events between 6 and 24 months. It would therefore be ideal to identify early on patients who will eventually need ICDs in order to maximize the benefit they can harvest from their implanted devices. Because DCM is a dynamic disease,[17] serial assessment of clinical and echocardiographic parameters may be helpful in discriminating between patients who are undergoing LVRR and those with a more morbid phenotype of the disease. In this study, the reduction of LVEDDi in the first 6 months of GDMT emerged as the strongest predictor of "late" LVEF improvement and thus as a potential tool for early risk stratification of future risk for MVAs or SCD. Other parameters, such as changes in MR, changes in RV dysfunction, and changes in restrictive filling pattern, surprisingly did not. This might reflect the fact that measurements of LVEDDi are not dependent on hemodynamic load and therefore might ultimately be more sensitive in capturing early reverse remodeling.[9,18] Further studies will be needed to define whether dynamic changes in LVEDDi could be combined with other features, such as genetic testing and presence of late gadolinium enhancement,[19,20] to effectively identify early patients who are at a higher risk for MVAs or SCD.

The present study highlights the challenge of defining the risk for MVAs or SCD in patients with DCM during the first 2 years of GDMT. This challenge raises the intriguing possibility of using wearable cardioverter defibrillators during this time. This would avoid the cost and morbidity associated with unnecessary ICD implantation without losing the protection offered by these devices. Dedicated studies will be needed to evaluate the safety and effectiveness of this potential strategy.[21]

Table 3 Univariable and multivariable predictors of "late" LVEF improvement (LVEF > 35%) at 24 months

	Univariable analysis		Multivariable analysis	
	Unadjusted odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
Age	0.99 (0.97-1.02)	.52		
Male sex	0.97 (0.42-2.24)	.95		
Familial DCM*	0.89 (0.33-2.43)	.82		
SBP	1 (0.98-1.03)	.57		
DBP	1 (0.96-1.05)	.73		
HR	1 (0.98-1.06)	.31		
NYHA functional class III or IV	1.23 (0.23-6.69)	.81		
Serum hemoglobin	0.86 (0.65-1.14)	.29		
Serum creatinine	0.63 (0.12-3.39)	.59		
LBBB	0.64 (0.26-1.60)	.34		
β-blockers	2.79 (0.71-11.06)	.10		
ACE inhibitors/ ARBs/ARNI	4.46 (0.78-25.49)	.09		
Loop diuretics	1 (0.47-2.29)	.91		
Digitalis	1.14 (0.43-3.06)	.79		
Duration of HF	0.96 (0.81-1.14)	.65		
RV systolic function normalization or persistence of normal RV function†	0.97 (0.33-2.87)	.96		
RFP disappearance†	2.28 (0.54-9.66)	.26		
MR improvement or persistence of mild/absent MR†	2.49 (1.11-5.58)	.02		
LVEF improvement†	1.18 (0.49-2.86)	.71		
LVEDDi reduction†	5.82 (1.6-20.69)	.007	4.92 (1.35-17.84)	.015
NYHA functional class improvement†	0.81 (0.15-4.41)	.81		

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor/neprilysin inhibitor; *DBP*, diastolic blood pressure; *HR*, heart rate; *LBBB*, left bundle branch block; *NYHA*, New York Heart Association; *RFP*, restrictive filling pattern; *SBP*, systolic blood pressure.

*At least one first-degree relative affected or SCD in a first-degree relative ≤35 years old.

†All dynamic parameters were evaluated as change from first evaluation to the 6-month time point evaluation. MR improvement refers to a reduction of MR grade from moderate or severe to mild or absent or the persistence of mild or absent MR. LVEDDi reduction is intended as a reduction of ≥10% or LVEDDi ≤ 33 mm/m^2.

Table 4 Relationship between MVAs or SCD after ≥24 months of follow-up and early LVEDDi reduction

	MVAs/SCD after 24 mo	No MVAs/SCD after 24 mo	Total
LVEDDi reduction	1 (4)	27 (96)	28
No LVEDDi reduction	13 (14)	78 (86)	91
Total	14 (12)	105 (88)	119

Data are expressed as number (percentage). P = .183 for comparison.

Study Limitations

We analyzed a well-characterized cohort of patients with DCM and provide several novel insights into the natural history of this disease. However, our study had some limitations that should be acknowledged. First, as an observational registry study, it suffers from common limitations of retrospective analyses; in particular, not all patients enrolled in the study had available echocardiograms at all the prespecified key time points, which resulted in different number of patients with echocardiograms at 6 and 24 months, and there were missing data. This could have introduced a selection bias.

Second, although we analyzed a cohort of consecutive patients, our strict inclusion criteria focused the analysis on only a fraction of the patients included in the HMDR. Third, although all MVAs were recorded and documented, SCD was adjudicated on the basis of clinical criteria.

Fourth, GDMT changed over the time span of this study, and therefore our study cohort might not perfectly represent the behavior of contemporary patients on current GDMT. Notably, patients across different periods of enrollment were equally well treated with β-blockers (91% of total population) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (97% of the total population; Supplemental Table 3). However, Although all patients in the cohort were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and β-blockers, our study cannot account for the effect of angiotensin receptor/neprilysin inhibitors and sodium-glucose cotransporter 2 inhibitors, only recently approved for the treatment of heart failure with reduced ejection fraction. Since their recent introduction in the standard therapy of heart failure with reduced ejection fraction, however, large cohort prognostic studies with long follow-up are lacking.

Fifth, our analysis may suffer from selection bias because (1) only the subset of patients surviving for the first 2 years of follow-up and with available measurements were considered in phase 2 of the study, and (2) landmark time points were chosen according to the standard distance between visits, but this could be considered a data-driven choice.

Sixth, because of the retrospective nature of this study, data on important prognosticators, such as late gadolinium enhancement detected by means of cardiac magnetic resonance or nonsustained ventricular arrhythmias detected by electrocardiographic monitoring, were not widely available and were therefore not included in the study. Finally, our results might not apply to specific patient categories, such as those with an arrhythmogenic phenotype of DCM, who have been recently recognized to have significant arrhythmic risk even in the absence of significant LV dysfunction.[22]

CONCLUSION

In response to GDMT, patients with DCM experience LVRR and improvement in LVEF for up to 2 years. Arrhythmic risk stratification on the basis of a single measurement of LVEF soon after the initiation of GDMT is therefore not effective in this patient population. We found that LVEF ≤ 35% becomes a valuable single parameter to stratify arrhythmic risk for patients with DCM after 2 years of GDMT. We also found that in unselected patients with DCM, the risk for adverse arrhythmic events is low during the first 2 years of treatment, suggesting that it might be appropriate to wait 24 months before deciding whether to implant an ICD. Further studies will be needed to confirm these findings and to confirm our observation that the reduction of LVEDDi during the first 6 months of treatment might be used to identify early patients who will experience late improvement of LVEF, which is associated with a lower risk for arrhythmic events. Until then, shared decision-making between patients and caregivers should be a key determinant of early referral of patients with DCM for ICD implantation.

ACKNOWLEDGMENTS

We would like to thank Fondazione CRTrieste, Fondazione CariGO, Fincantieri, and all the health care professionals of Azienda Sanitaria Universitaria Giuliano Isontina for their continuous support of the clinical management of patients affected by cardiomyopathies within the Heart Failure Outpatient Clinic of Trieste.

SUPPLEMENTAL MATERIAL

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2019.01.007.

REFERENCES

1. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.
3. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221-30.
4. Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. J Am Coll Cardiol 2011;57:1468-76.
5. Al-Khatib SM, Hellkamp A, Curtis J, Mark D, Peterson E, Sanders GD, et al. Non-evidence-based ICD implantations in the United States. JAMA 2011;305:43-9.
6. Merlo M, Cannatà A, Pio Loco C, Stolfo D, Barbati G, Artico J, et al. Contemporary survival trends and aetiological characterization in non-ischaemic dilated cardiomyopathy. Eur J Heart Fail 2020;22:1111-21.
7. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Bohm M, et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J 2016;37:1850-8.
8. Merlo M, Caiffa T, Gobbo M, Adamo L, Sinagra G. Reverse remodeling in Dilated Cardiomyopathy: insights and future perspectives. Int J Cardiol Hear Vasc 2018;18:52-7.
9. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography

and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.
10. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.
11. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611-44.
12. Merlo M, Gobbo M, Stolfo D, Losurdo P, Ramani F, Barbati G, et al. The prognostic impact of the evolution of RV function in idiopathic DCM. JACC Cardiovasc Imaging 2016;9:1034-42.
13. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials. Circulation 2015;132:302-61.
14. Spezzacatene A, Sinagra G, Merlo M, Barbati G, Graw SL, Brun F, et al. Arrhythmogenic phenotype in dilated cardiomyopathy: natural history and predictors of life-threatening arrhythmias. J Am Heart Assoc 2015;4:e002149.
15. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141-54.
16. Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, et al. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the America. Circulation 2008;52:1179-99.
17. Stolfo D, Ceschia N, Zecchin M, De Luca A, Gobbo M, Barbati G, et al. Arrhythmic risk stratification in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2018;121:1601-9.
18. Strohm O, Schulz-Menger J, Pilz B, Osterziel KJ, Dietz R, Friedrich MG. Measurement of left ventricular dimensions and function in patients with dilated cardiomyopathy. J Magn Reson Imaging 2001;13:367-71.
19. Di Marco A, Anguera I, Schmitt M, Klem I, Neilan TG, White JA, et al. Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. JACC Heart Fail 2017;5:28-38.
20. Arbustini E, Disertori M, Narula J. Primary prevention of sudden arrhythmic death in dilated cardiomyopathy. JACC Heart Fail 2017;5:39-43.
21. Barsheshet A, Kutyifa V, Vamvouris T, Moss AJ, Biton Y, Chen L, et al. Study of the wearable cardioverter defibrillator in advanced heart-failure patients (SWIFT). J Cardiovasc Electrophysiol 2017;28:778-84.
22. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. Heart Rhythm 2019;16:e301-72.

Supplemental Table 1 Characteristics at enrollment of patients with LVEFs ≤ 35% at 6-month evaluation and echocardiographic data available at the 24-month evaluation, divided according to LVEF at 24 months (phase 2 of the study)

	Total	LVEF > 35% at 24 mo	LVEF ≤ 35% at 24 mo	
	(*N* = 131)	(*n* = 88)	(*n* = 43)	*P*
Age, y	53 ± 14	52 ± 14	53 ± 14	.29
Sex, male	97 (74.0)	65 (73.9)	32 (74.4)	.95
Familial DCM*	20 (15.3)	13 (14.8)	7 (16.3)	.82
Symptom duration at enrollment, mo	1.7 ± 2.0	1.6 ± 1.9	1.8 ± 2.4	.66
SBP, mm Hg	122 ± 16	123 ± 16	120 ± 16	.29
DBP, mm Hg	77 ± 10	78 ± 10	76 ± 12	.43
HR, beats/min	84 ± 18	85 ± 19	81 ± 15	.22
NYHA functional class III or IV	47 (37.6)	30 (35.7)	17 (41.5)	.53
LVEF, %	24 ± 6	24 ± 6	23 ± 7	.57
LVEDDi, mm/m^2	36 ± 5	36 ± 5	36 ± 5	.98
LVESDi, mm/m^2	31 ± 8	30 ± 9	33 ± 5	.11
RFP	41 (32.5)	30 (35.3)	11 (26.8)	.34
Moderate to severe MR	59 (46.1)	37 (43.0)	22 (52.4)	.32

Data are expressed as mean ± SD or as number (percentage).
DBP, Diastolic blood pressure; *HR*, heart rate; *LVESDi*, indexed LV end-systolic diameter; *NYHA*, New York Heart Association; *RFP*, restrictive filling pattern; *SBP*, systolic blood pressure.
*At least one first-degree relative affected or SCD in a first-degree relative ≤35 years old.

Supplemental Table 2 Relationship between early LVEDDi reduction and late LVEF improvement

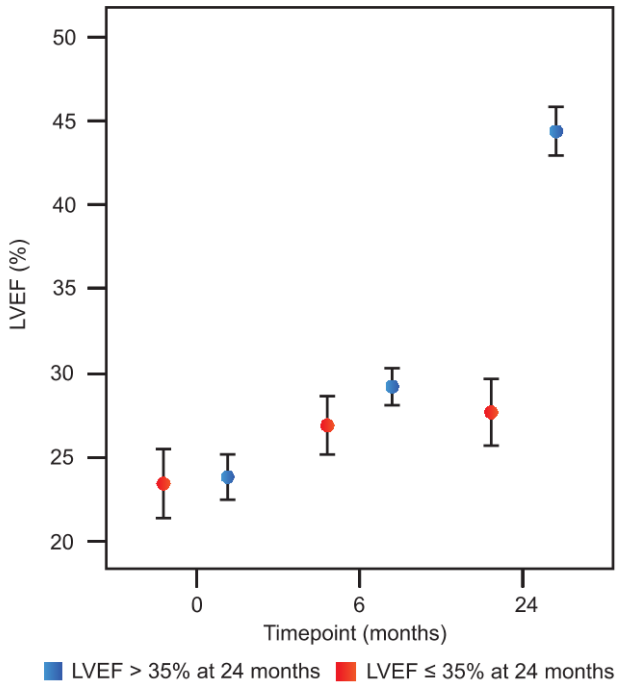
	Total	Late LVEF improvement	No late LVEF improvement
LVEDDi reduction	28	25 (89)	3 (11)
No LVEDDi reduction	91	53 (58)	38 (42)
Total	119	78 (66)	41 (34)

Data are expressed as number (percentage). *P* = .003 for comparison.

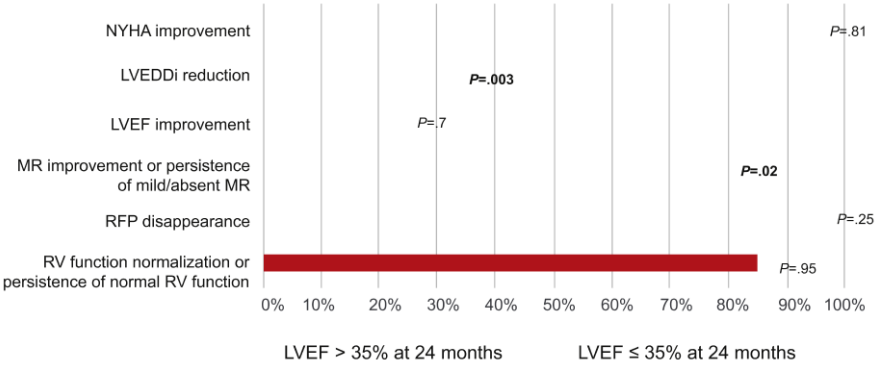
Supplemental Table 3 Characteristics at enrollment of study population divided according to years of enrollment

	1993-1997 (*n* = 97)	1998-2002 (*n* = 82)	2003-2007 (*n* = 132)	2008-2012 (*n* = 115)	2013-2017 (*n* = 118)
Age, y	43 ± 14	42 ± 13	51 ± 13	54 ± 15	55 ± 12
Sex, male	70 (72)	64 (78)	89 (67)	79 (69)	83 (70)
NYHA functional class III or IV	20 (21)	19 (23)	37 (34)	35 (31)	33 (28)
ACE inhibitors/ARBs/ARNIs	95 (98)	79 (96)	122 (95)	113 (98)	113 (97)
β-blockers	86 (89)	73 (89)	119 (93)	101 (88)	110 (94)
LVEF, %	32 ± 10	31 ± 10	31 ± 10	31 ± 9	28 ± 10
LVEF ≤ 35% at enrollment	67 (69)	55 (67)	97 (74)	82 (71)	99 (84)
LVEDDi, mm/m^2	36 ± 6	35 ± 6	34 ± 5	33 ± 4	34 ± 5

Data are expressed as mean ± SD or as number (percentage).
ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *ARNI*, angiotensin receptor/neprilysin inhibitor; *NYHA*, New York Heart Association.



Supplemental Figure 1 Mean LVEF at enrollment, 6 months, and 24 months in patients with or without subsequent "late" LVEF improvement (phase 2 of the study). Note that patients with "late" LVEF improvement (i.e., LVEF ≤ 35% at 6-month evaluation and LVEF > 35% at 24-month evaluation) reached a mean value of LVEF of 44% at 24-month evaluation.



Supplemental Figure 2 Proportion of patients with improvements in various dynamic parameters from enrollment to 6 months, stratified by subsequent "late" LVEF improvement (phase 2 of the study). Each parameter reported was defined comparing data collected at 6 months and data collected at enrollment. *Red bars* represent observations made in patients who did not experience improvement in LVEF to >35% between 6 and 24 months. The *blue bars* represent observations made in patients who instead experienced "late" LVEF improvement. *NYHA*, New York Heart Association; *RFP*, restrictive filling pattern.